CRITICAL CARE

REVIEW

Clinical review: Probiotics in critical care

Neil H Crooks*[1], Catherine Snaith[1], Deborah Webster[2], Fang Gao[3] and Peter Hawkey[4,5]

Abstract

Patients in ICUs represent a relatively small subgroup of hospitalised patients, but they account for approximately 25% of all hospital infections. Approximately 30% of ICU patients suffer from infection as a complication of critical illness, which increases the length of ICU stay, morbidity, mortality and cost. Gram-negative bacteria are the predominant cause of ICU-related infections and with the rise in multidrug-resistant strains we should focus our attention on nonantibiotic strategies in the prevention and treatment of nosocomial infections. Probiotics have been proposed as one option in this quest; however, mechanisms of action in the critically ill population require further investigation. Some of the beneficial effects appear to be associated with improvement in gastrointestinal barrier function, restoration of normal intestinal permeability and motility, modification of the balance of intestinal microbiota and immunomodulation. However, the information we have to date on the use of probiotics in the critical care setting is difficult to interpret due to small sample sizes, differences in ICU populations, the variety of probiotic combinations studied and differences in administration techniques. In this review we shall examine the use of probiotics in the critical care setting, look at some of the proposed mechanisms of action and discuss their potential benefits and drawbacks.

Introduction

During an episode of critical illness a number of significant changes occur in the microbiota of the human gut. These changes occur due to alterations in the stress hormone profile, impairment of blood supply to the gut, immunosuppression, antibiotic use and nutrient deficiency [1]. In experimental models these changes have been shown to occur within 6 to 8 hours, with endogenous *Lactobacillus* strains being replaced by pathogenic bacteria [2]. This change can lead to a breakdown in the intestinal barrier function that is likely to play a significant role in the pathogenesis of multiple organ dysfunction syndrome [3,4].

Redressing this balance and exploiting the beneficial effects of probiotic bacteria is understandably an area of considerable interest. However, the mechanisms by which these microorganisms exert their effects are various and depend upon the dose used, the route(s) of administration and the dosing frequency [5]. Furthermore, a number of these effects are strain specific.

Probiotics, prebiotics and synbiotics

Probiotics are defined as 'live microorganisms that confer a health benefit on the host when administered in adequate amounts' [6]. Prebiotics are nondigestible food components that stimulate the growth and/or activity of bacteria in the digestive tract in ways that may be beneficial to health [7]. Synbiotics are a combination of probiotics and prebiotics. There has been an explosion of interest in probiotics and their potential health benefits since 2000, with initial attention focusing on the gastrointestinal tract.

Probiotics and the gastrointestinal tract

The human intestine is home to hundreds of species of bacteria, archaea and eukarya, many of which are nonculturable but can now be identified using metagenomic approaches. The bacterial load tends to be highest in the large intestine (up to 10^{11} colony-forming units/g), and while the healthy human gut is dominated by *Bacteroides*, *Firmicutes* and *Actinobacteria*, each individual has their own distinct stool bacterial composition determined by environmental and genetic factors. This bacterial profile remains relatively constant over time unless altered by disease state or antibacterial treatment [8,9].

Culture-based and molecular detection methods have demonstrated that it is possible to significantly alter the composition of gut flora in adults and infants by treatment with probiotics. Sepp and colleagues treated 15 neonates with *Lactobacillus rhamnosus* GG for the first

*Correspondence: nhcrooks@gmail.com
[1]Academic Department of Anaesthesia, Critical Care and Pain, Heart of England NHS Foundation Trust, Birmingham Heartlands Hospital, Bordesley Green East, Birmingham B9 5SS, UK
Full list of author information is available at the end of the article

2 weeks of life. They found that *L. rhamnosus* GG persisted for 1 month in eight of these neonates. There were also significant differences in the bacterial composition of the stool compared with the control group, with increased numbers of coliforms, lactobacilli and *Bifidobacterium* spp. [10]. Benno and colleagues demonstrated a statistically significant increase in bifidobacteria in adults treated with *L. rhamnosus* GG for a 4-week period. They also found an increase in lactobacilli and a decrease in the proportion of *Clostridium* spp. [11]. As these techniques are based on faecal profiling, they tend to reflect the large bowel bacterial composition with little information being available on the small bowel effects of probiotics.

Mechanisms of action of probiotics

Much of the information available on the mechanisms of action of probiotics is obtained from animal work and *in vitro* studies; hence we must be careful in extrapolating this to humans. What is clear, however, is that there are multiple mechanisms by which different probiotic bacteria exert their effects, and these effects may vary with the strain and population studied. Table 1 summarises the main mechanisms by which probiotics exert their effects, and Table 2 presents details of commonly used probiotic preparations.

Probiotics may alter the local environment within the lumen of the gut, producing antimicrobial effects on pathogenic organisms. Lactic acid-producing and acetic acid-producing probiotics reduce the luminal pH resulting in an unfavourable milieu for pathogens. This has been demonstrated *in vitro* with pathogen growth being reduced in a pH-dependent manner by *Lactobacillus* spp. [12]. Venturi and colleagues demonstrated a significant reduction of luminal pH *in vivo* in ulcerative colitis patients treated with the probiotic mixture VSL#3 [13].

Probiotics also exert a direct antimicrobial effect via the production of bacteriocins. Bacteriocins are proteins produced by bacteria that inhibit the growth and virulence of other pathogenic bacteria. Probiotic bacteria deficient in the bacteriocin gene are less effective probiotics, as demonstrated in a murine model where a mutant form of *Lactobacillus salivarius* UCC118 failed to protect against infection with *Listeria monocytogenes* [14]. A wide variety of bacteriocins is recognised, and their spectrum of action ranges from antagonism of similar bacterial strains to the inhibition of a wide range of Gram-positives, Gram-negatives, yeasts and moulds [15]. One such example of a broad-spectrum bacteriocin is that produced by a subspecies of *L. salivarius*. The ABP-118 bacteriocin inhibits *Bacillus*, *Staphylococcus*, *Enterococcus*, *Listeria* and *Salmonella* spp. [16].

Bacteria communicate with each other using a mechanism known as quorum sensing. This involves the production and secretion of signalling molecules known as autoinducers. In their *in vitro* study, Medellin-Peña and colleagues demonstrated that *Lactobacillus acidophilus* La-5 secretes molecules that disrupt this interbacterial communication, reducing expression of virulence-related genes by *Escherichia coli* O157:H7 [17].

Probiotics have also been demonstrated to enhance intestinal barrier function. Intestinal barrier function is complex and its control involves cellular stability at a cytoskeletal and tight junction level, as well as mucus, chloride and water secretion. Probiotics have been shown to exert an effect, *in vitro* and *in vivo*, via these mechanisms [15]. For example, *Lactobacillus plantarum* 299v can enhance mucus production and secretion in human intestinal epithelial cells [18]. The probiotic strain *E. coli* Nissle 1917 appears to enhance mucosal barrier function by production of human β-defensin 2 [15]. *E. coli* Nissle has also has been demonstrated *in vitro* to reduce adhesion and invasion of intestinal epithelial cells by an enteroinvasive *E. coli.*

In addition, by competing with pathogens for nutrients and adhesion in a microbiological niche, probiotics can prevent replication by pathogens, a phenomenon known as colonisation resistance [5]. Probiotics can thus promote the integrity of the gut defence barrier and create an unfavourable environment for pathogen colonisation.

Probiotics can also exert a range of immunological effects. The interaction between the luminal bacteria and the underlying epithelial and mucosal lymphoid cells is referred to as bacterial–epithelial cross-talk. This cross-talk enables probiotics to have an effect on both the innate and adaptive host immune system [19] – for example, promotion of B cells into plasma cells, increased production of secretory immunoglobulin A and prevention of activation of the proinflammatory nuclear transcription factor NF-κB [5]. Other immunologic mechanisms include alteration of the cytokine profile and activation of macrophages to present antigen to B lymphocytes and increase immunoglobulin production [20].

Probiotics in the critically ill

The efficiency of intestinal barrier function is demonstrated by the fact that the faecal bacterial concentration approaches 10^{12} organisms/ml in the caecum, while tissues one cell deep to the intact intestinal mucosa are usually sterile [21]. Any significant insult to the gut or alteration to its microbiota is likely to play a role in promoting systemic inflammation and infection in the critically ill population [22]. In contrast to the large bowel, the stomach, duodenum and jejunum have a relative paucity of bacteria (10^3 to 10^4 organisms/ml). The presence of enteric organisms in gastric aspirates is therefore abnormal and represents gastric colonisation. In the context of critical illness, this colonisation is the result of bacterial overgrowth in the proximal gastrointestinal tract [21].

Table 1. Summary of mechanisms of action for probiotics

Mechanism of action		Specific probiotic examples
Luminal pH modification	Production of lactic acid and acetic acid reduces luminal pH resulting in unfavourable milieu for pathogens	*Lactobacillus* spp.: pH-dependent reduction in pathogen growth [12]
		VSL#3: *in vivo* luminal pH reduction in ulcerative colitis patients [13]
Bacteriocin production	Bacteriocins are proteins produced by bacteria that inhibit the growth and virulence of other microorganisms. The may be narrow spectrum (inhibit related bacterial strains) or broad spectrum (inhibit a wide range of bacteria, yeasts and moulds) [15]	Mutant *Lactobacillus salivarius* deficient in bacteriocin gene are unable to protect mice against *Listeria monocytogenes* infection [14]
		L. salivarius subspecies produce broad-spectrum bacteriocins [16]
Disruption of interbacterial communication	Autoinducers are the signalling molecules produced and secreted by bacteria that form the basis of quorum sensing (bacterial communication)	*Lactobacillus acidophilus* La-5 disrupts quorum sensing and expression of virulence-related genes by *Escherichia coli* O157:H7 [17]
Enhanced mucosal barrier function	Increased intestinal epithelial cell mucus production and secretion	*Lactobacillus plantarum* 299v: increased mucin gene expression *in vitro* [18] and adherence to colonic cells via a mannose-specific adherence mechanism [74]
	Reduced adhesion and invasion of intestinal epithelial cells by enteroinvasive bacteria resulting in reduced translocation	*Lactobacillus casei rhamnosus* adheres to colonic cells *in vitro* [75]
	Increased production of human β-defensin 2 by epithelial cells	*E. coli* Nissle 1917: increase in mucin gene expression [76] and production of human β-defensin 2 by colonic cells [77]
	Stabilisation of intracellular tight junctions and reduced chloride/water secretion	*Streptococcus thermophiles* and *L. acidophilus* reduce water and chloride secretion in response to pathogenic bacteria [78,79]
	Epithelial cell regeneration and reduced apoptosis	*Lactobacillus* pretreatment of intestinal epithelium reduces disruption of epithelial tight junctions by pathogenic *E. coli* [80]. Probiotic preparation VSL#3 (see Table 2) prevents redistribution of epithelial tight junction proteins on exposure to pathogenic bacteria [76]. *Lactobacillus rhamnosus* GG prevents cytokine-mediated apoptosis of intestinal epithelial cells [81]. *Lactobacillus casei* and *Clostridium butyricum* both stimulate gut epithelial proliferation in rats [82]
Colonisation resistance	The probiotic competes with pathogen for nutrients and adhesion in a microbiological niche [5]	*L. casei rhamnosus* adheres to colonic cells, reduces pathogenic bacterial growth and can persist within the gastrointestinal tract [75,83]
		E. coli Nissle 1917 inhibits growth of Shiga-toxin producing *E. coli* [84]
Immunological effects	Bacterial–epithelial cross-talk enables luminal probiotic organisms to influence gut-associated lymphoid tissue and innate and adaptive host responses [19,85]. Toll-like receptors play a central role in mediating this process [86]	VSL#3 has been associated with increased anti-inflammatory and reduced proinflammatory cytokine activity, reduced inducible nitric oxide synthase and matrix metalloproteinase activity in patients with pouchitis [87]. *L. plantarum* 299v increases IL-10 secretion from macrophages and T cells in patients with ulcerative colitis [88]. *L. casei* and *Lactobacillus bulgaricus* significantly reduce TNFα release from inflamed mucosa in Crohn's disease [89]. *E. coli* Nissle 1917 shows local and systemic anti-inflammatory effects in a murine model of lipopolysaccharide-induced sepsis [90]
	Increased promotion of B cells to plasma cells and increased production of immunoglobulins [5]	*L. rhamnosus GG*: increased circulating IgA, IgG and IgM concentrations in children with gastroenteritis [91,92]. Pretreatment with probiotic prior to typhoid vaccination leads to increased anti-typhoid antibody titres [93]
	Activation and modulation of macrophages, T cells and natural killer cells	*L. casei* Shirota: cell wall structure potently induces IL-12 production and the probiotic differentially controls the inflammatory cytokine responses of macrophages, T cells and natural killer cells [30,94,95]. *L. casei* Shirota and *Bifidobacterium breve* administered preoperatively to biliary cancer patients significantly reduce postoperative IL-6, C-reactive protein and white cell count concentrations [30]. *L. acidophilus* and *Bifidobacterium longum* increased macrophage phagocytic activity in a murine model [96]

Colonisation of the stomach by pathogens or potential pathogens is believed to occur due to a combination of poor gut motility, increased gastric pH (due to acid suppression) and the use of broad-spectrum antibiotics. This combination of factors leads to an overgrowth of bacteria in the duodenum, which reflux into the stomach and are ultimately regurgitated and aspirated into the lungs [23].

The normal intestinal microbiota of critically ill patients is altered and replaced by pathogens for a number of reasons. Therefore, it would seem logical to consider that probiotics may have a role in reducing intestinal

Table 2. Summary of probiotic preparations

Probiotic	Constituents	Administration example and dosing comments
Antibiophilus (Lcr35) (Germania Pharmazeutika GesmbH, Vienna, Austria)	*Lactobacillus casei rhamnosus*	10^9 CFU twice daily via nasogastric tube [75]
Ecologic 641 (Winclove Bio Industries, Amsterdam, the Netherlands)	Six different strains of bacteria: *Lactobacillus acidophilus*, *Lactobacillus casei*, *Lactobacillus salivarius*, *Lactococcus lactis*, *Bifidobacterium bifidum*, and *Bifidobacterium lactis* (previously classified as *Bifidobacterium infantis*), plus cornstarch and maltodextrins	Administered twice daily via nasojejunal tube to a total daily dose of 10^{10} bacteria [35]
Ergyphilus (Nutergia, Capdenac, France)	Predominantly *Lactobacillus rhamnosus* GG, but also *L. casei*, *L. acidophilus* and *B. bifidum*	One capsule contains 2×10^{10} lyophilised bacteria. Capsules can be broken and given via enteral feeding tube. Five capsules administered over 24 hours in critically ill patients [53]
Mutaflor (Ardeypharm GmbH, Herdecke, Germany)	*Escherichia coli* Nissle 1917	2.5×10^9 to 25×10^9 bacteria per capsule. Adult dose 1 or 2 capsules per day [97]
Proviva (Skanemejerier, Malmo, Sweden)	*Lactobacillus plantarum* 299v and oatmeal	Oatmeal-based drink containing 5×10^7 CFU/ml. Dose of 500 ml used by McNaught and colleagues [24]
Synbiotic 2000 (Medipharm, Kagerod, Sweden and Des Moines, IA, USA)	A probiotic mixture comprising *Pediacoccus pentosaceus* 5-33:3, *Leuconostoc mesenteroides* 77:1, *Lactobacillus paracasei* ssp., paracasei F19, *L. plantarum* 2362 plus β-glucan, inulin, pectin and resistant starch	Administered twice daily via feeding tube or orally [32]
Synbiotic 2000 Forte (Medipharm, Kagerod, Sweden and Des Moines, IA, USA)	A probiotic mixture comprising *P. pentosaceus* 5–33:3, *L. mesenteroides* 32–77:1, *L. paracasei* ssp. paracasei 19 and *L. plantarum* 2362, plus inulin, oat bran, pectin and resistant starch	Sachet for reconstitution containing 10^{10} each bacteria plus 10 g prebiotic fibre. Administered in doses of 12 g (1 sachet) per day for a 15-day study period [47]
Trevis (Christen Hansen, Hørsholm, Denmark)	*L. acidophilus* La5, *Lactobacillus bulgaricus*, *B. lactis* Bb-12 and *Streptococcus thermophilus*	4×10^9 CFU/capsule. One capsule three times daily [25,26]
VSL#3 (Ferring Pharmaceuticals, West Drayton, UK)	Four strains of *Lactobacillus* (*L. acidophilus*, *L. casei*, *L. plantarum*, *Lactobacillus delbrueckii*), three strains of *Bifidobacterium* (*B. infantis*, *Bifidobacterium longum*, *Bifidobacterium breve*) and one strain of *Streptococcus salivarius* subsp. *Thermophilus*	Powder for reconstitution with water or to be mixed with cold foods prior to consumption. One sachet contains 4.5×10^{11} lactic acid bacteria. Also available as a capsule containing 2.25×10^{11} bacteria Adult dose 0.5 to 8 sachets (2 to 32 capsules) per day depending upon disease activity. Six grams once a day for 12 months administered by Venturi and colleagues [13]

CFU, colony-forming units.

colonisation by pathogens and thus in the prevention of infection and sepsis syndromes in this population.

Probiotics in the prevention of nonrespiratory infection

Probiotics have been studied in the prevention of postoperative infection. Three studies in patients undergoing major colorectal surgery have shown no significant reduction in postoperative infection rates [24-26]. In each study, however, the effectiveness may have been limited by a relatively short postoperative period of probiotic administration (4 to 5 days). In contrast, several studies in patients undergoing pancreatic resection [27,28] and hepatic resection [29,30] have shown significant reductions in postoperative infection rates of up to 30%. These patients received probiotic for 8 to 14 days postoperatively.

Liver transplant patients have multiple risk factors for infection, including profound immunosuppression. Two randomised trials have shown probiotics to be safe and effective in this group of patients. In the first study 95 patients were randomised to receive standard enteral feed plus selective bowel decontamination, fibre-containing enteral feed plus live *L. plantarum* 299 (Lp299) or fibre-containing enteral feed plus heat-killed Lp299 [31]. The live Lp299 group developed significantly fewer infections than the other two groups (48% vs. 13% vs. 34%, respectively). In addition, the mean duration of antibiotic

therapy, the mean total hospital stay and the length of ICU stay were also shorter than in the groups with inactivated Lp299 and selective bowel decontamination. However, these differences did not reach statistical significance. The second study compared only Synbiotic 2000 and prebiotic fibre, reporting postoperative infection rates of 3% and 48%, respectively [32]. No serious side effects or infections caused by the probiotics were noted in either study.

Oláh and colleagues randomised 45 patients with severe acute pancreatitis to receive enteral oat fibre and live Lp299 or enteral oat fibre and heat-killed Lp299 [33]. In the group treated with the live probiotic, only one patient required surgery for a septic complication involving the pancreas, compared with seven such complications in the control group (P = 0.02). There was also a nonsignificant trend toward a shorter length of hospital stay (13.7 days vs. 21.4 days, respectively). The same group carried out a single-centre, double-blind, randomised placebo-controlled trial using Synbiotic 2000 in a further 62 patients with severe acute pancreatitis [34]. This trial showed no statistically significant differences in the incidence of mortality, septic complications or development of multiorgan failure between the two groups. However, the total incidence of systemic inflammatory response syndrome, multiple organ failure and rate of complications was significantly less in the treatment group versus the control group (8 vs. 14, P <0.05 and P <0.05, respectively).

The trial that has raised most concern with regard to adverse outcomes and the use of probiotics is the PROPATRIA trial [35]. In this multicentre, placebo-controlled trial, 296 patients with predicted severe acute pancreatitis were randomised to receive the synbiotic preparation Ecologic 641 or placebo. This was administered together with fibre-enriched enteral feed via the nasojejunal route for 28 days. The rate of infectious complications was similar in both groups (30% vs. 28%) but the mortality rate was higher in the synbiotic group. Nine patients in the synbiotic group developed bowel ischaemia, eight of these being small bowel ischaemia. There were no cases of bowel ischaemia in the placebo group. One possible explanation for this outcome is a difference in the two groups, with more patients in the synbiotic group having established organ failure at the time treatment began. Another theory is that such a significant intestinal burden of bacteria and high-fibre feed could result in increased oxygen consumption and local bowel ischaemia. Nevertheless, this is the first time such a complication has been reported.

Probiotics in the prevention of respiratory infection

The respiratory tract is consistently the most common site of nosocomial infection, accounting for 65% of ICU-acquired infections [36]. Ventilator-associated pneumonia (VAP) complicates the care of up to 30% of patients receiving mechanical ventilation, accounting for 50 to 60% of total antibiotic days [37-40]. Patients with VAP present increased morbidity and mortality, prolonged ICU and hospital lengths of stay, and increased costs [41].

Current VAP prevention strategies aim to reduce colonisation of the oropharynx and upper gastrointestinal tract with pathogenic bacteria and prevent their subsequent aspiration. These measures include elevation of the head of the bed, silver-coated tracheal tubes, oral care, subglottic secretion drainage and use of sedation breaks and weaning protocols. Selective digestive tract decontamination using antibiotics in the oral cavity or whole gastrointestinal tract decontamination have been shown to reduce rates of VAP and mortality [42,43]. However, these strategies have not gained widespread favour in critical care owing to concerns about promoting antibiotic resistance. Oostdijk's group demonstrated a statistically significant increase in intestinal colonisation with Gram-negative bacteria resistant to ceftazidime, tobramycin or ciprofloxacin (P <0.05) [44]. These concerns were also borne out by a large-cluster, randomised cross-over study of selective decontamination of the digestive tract that showed a marked increase resistance to ceftazidime in faecal *Enterobacteriaceae*, together with a small but significant increase in bacterial resistance from the respiratory tract [45]. In a previous study, the use of cefotaxime as part of selective decontamination of the digestive tract regime was found to select for an outbreak of extended-spectrum β-lactamase-producing *E. coli* and *Klebsiella pneumonia* [46].

To date there have been eight randomised controlled trials of probiotic therapy as a strategy to prevent VAP [38,47-53]. The inclusion criteria, sample size (range 50 to 348), populations studied and diagnostic criteria for VAP varied between studies. The probiotic formula, dosing and route of administration also varied but all trials contained *Lactobacillus* spp. (see Table 3). Six of the eight trials showed a lower incidence of VAP in the probiotic group [38,47,48,50–52], but this difference was statistically significant in only three of the studies [38,47,48]. Interestingly, one study used chlorhexidine oral disinfection as a control and found that probiotic Lp299 was at least as effective in preventing oropharyngeal colonisation (61.9% vs. 34.8% new colonisation, respectively; P = 0.13) [50]. The study by Forestier and colleagues found no difference in incidence of VAP between groups but did demonstrate a median delay in respiratory colonisation with *Pseudomonas aeruginosa* of 50 days versus 11 days in controls (P = 0.01) [49]. This is the most commonly isolated antibiotic-resistant Gram-negative species in VAP [39].

Table 3. Probiotic trials in mechanically ventilated patients for prevention of ventilator-associated pneumonia/respiratory tract infection

Study	*n*	Study design	Study population	Probiotic regimen	Primary endpoint	Additional findings	Limitations
VAP/respiratory tract infection as primary outcome							
Forestier and colleagues [49]	208	DB, SC, RCT	Mixed ICU, >18 years old, requiring MV >48 hours	*Lactobacillus casei rhamnosus*, 10^9 CFU vs. placebo ng/og twice daily until ICU discharge or death	Time to first colonisation/infection of the gastric and respiratory tracts with *Pseudomonas aeruginosa* strains. Median delay 50 days probiotic vs. 11 days placebo ($P = 0.01$)	*P. aeruginosa* VAP reduced in probiotic group: 2.9% vs. 7.5% (P = NS). No adverse effects	Single centre. More patients in probiotic group than placebo received antipseudomonal antibiotics during their admission (55% vs. 43%)
Knight and colleagues [51]	259	DB, SC, RCT	Mixed ICU, >16 years old, requiring MV >2 days	Synbiotic 2000 Forte: 10^{10} CFU vs. placebo ng/og twice daily until day 28, ICU discharge or death	Incidence of VAP: 9% probiotic vs. 13% placebo ($P = 0.42$)	Hospital mortality: 27% vs. 33% ($P = 0.39$). No adverse effects	Single centre. Overall VAP rate lower than anticipated
Morrow and colleagues [38]	146	DB, SC, RCT	Mixed ICU, >18 years old, expected to require MV >72 hours	*Lactobacillus rhamnosus* GG 10^9 CFU vs. placebo per orally and ng twice daily, started within 24 hours until death, extubation or tracheostomy	Incidence of VAP: 19.1% probiotic vs. 40% placebo ($P = 0.007$)	Significant reduction in *Clostridium difficile*-associated diarrhoea and ICU-associated diarrhoea, fewer antibiotic days, delay in onset of VAP, reduction in gastric and oral colonisation with pathogenic species, preferential reduction in VAP caused by Gram-negative pathogens. No adverse effects	Single centre. Small sample size. High-risk population, selected: mean APACHE II score 23, mean days ventilated 10 days. Extensive exclusions: pregnancy; immunosuppression; prosthetic heart valve or vascular graft; cardiac trauma; history of rheumatic fever, endocarditis or congenital heart defect; gastro-oesophageal or intestinal injury or foregut surgery; oropharyngeal injury; tracheostomy
VAP/respiratory tract infection as secondary outcome							
Kotzampassi and colleagues [47]	65	DB, two centre, RCT	Severe multiple trauma patients, >18 years old, requiring MV	Synbiotic 2000 Forte: 10^{11} CFU vs. placebo once daily via gastrostomy or ng for 15 days	Systemic infection rate during ICU stay or the development of SIRS and MODS. Overall infection rate: 63% probiotic vs. 90% placebo ($P = 0.01$)	VAP rate reduced in probiotic group: 54% vs. 80% in placebo group ($P = 0.03$). Central line and urinary tract infections also significantly reduced. Severe sepsis: 17% vs. 40% ($P = 0.04$). Ventilation days ($P = 0.001$) and ICU length of stay ($P = 0.01$) significantly reduced with probiotics. Reduction in mortality (14.3% vs. 30%) nonsignificant ($P = 0.12$). No adverse effects	Small sample size, severe trauma patients only
Spindler-Vessel and colleagues [48]	132	SC, RCT	Severe multiple-trauma patients requiring MV, at least 4-day ICU stay	Synbiotic 2000 Forte, 10^{10} CFU vs. glutamine or fermentable fibre or peptide diet once daily ng/og for 15 days or until ICU discharge or death	Effect on intestinal permeability reduced on day 7 in probiotic group only ($P < 0.05$)	Probiotic group also had fewer pneumonias ($P = 0.03$) and total infections ($P = 0.003$). No adverse effects	Single centre. Small sample size, comparing multiple interventions, no placebo group

Continued overleaf

Table 3. Continued

Study	*n*	Study design	Study population	Probiotic regimen	Primary endpoint	Additional findings	Limitations
VAP/respiratory tract infection as secondary outcome (continued)							
Klarin and colleagues [50]	50	Open label, SC, RCT	Mixed ICU, 18 years old, requiring MV >24 hours	*Lactobacillus plantarum* 299, 10^{10} CFU vs. 0.1% chlorhexidine per orally twice daily until ICU discharge or death	Pathogenic bacterial load in oropharynx. New colonisation rate: 34.8% probiotic vs. 61.9% chlorhexidine ($P = 0.13$)	Emerging bacteria largely Gram-negative species. Noncolonised patients had lower ventilator days ($P < 0.001$). Incidence of VAP: 4% probiotic group vs. 14% chlorhexidine group (P = NS). No adverse effects	Single centre. Not powered for incidence of VAP as primary outcome. Small sample size
Barraud and colleagues [53]	167	DB, SC, RCT	Medical ICU, >18 years old, MV > 48 hours	Ergyphilus $2x10^{10}$ lactic acid bacteria, mostly *L. rhamnosus* GG, once a day vs. placebo via enteral feeding tube.	28-day mortality. No difference: 25.3% probiotic vs. 23.7% placebo ($P = 0.8$)	Mortality rates in ICU and at 90 days were also unaffected by the treatment. Incidence of ICU-acquired infections including VAP not significantly different except for catheter-related bloodstream infections that were lowered by probiotics. Reduced 28-day mortality in severe sepsis patients given probiotics ($P = 0.035$) but higher mortality rate in nonsevere sepsis patients ($P = 0.08$)	Single centre. Small sample. Stopped early
Oudhuis and colleagues [52]	254	Two centre, open label, cross over	Mixed ICUs, consecutive ICU patients with expected MV ≥48 hours and/or expected ICU stay ≥72 hours	*L. plantarum* 299/299v in a dose of $5x10^9$ CFU together with 6 g of rose-hip, twice daily via ng vs. SDD	ICU-acquired infection rate: 31% probiotic vs. 24% SDD ($P = 0.10$)	No significant difference in VAP rate (7.7% vs. 7.2%.), 28-day or ICU mortality between groups	Small sample size. Stopped early. Crossover of units was not completed, resulting in unequal mix of patients and disease burden. Not DB. Infections defined retrospectively

APACHE, Acute Physiology and Chronic Health Evaluation; CFU, colony-forming units; DB, double blind; MODS, multiorgan dysfunction syndrome; MV, mechanical ventilation; ng, nasogastric; NS, not significant; og, orogastric; RCT, randomised controlled trial; SC, single centre; SDD, selective decontamination of digestive tract; SIRS, systemic inflammatory response syndrome; VAP, ventilator-associated pneumonia.

Conflicting results also arise from meta-analyses of probiotics in critical care. The work by Watkinson and colleagues in 2007 analysed the use of prebiotics, probiotics and synbiotics in 999 adult critical care patients from eight randomised controlled trials and concluded that there was no benefit in the probiotic prophylaxis of VAP [54]. In 2010, however, Siempos and colleagues examined five randomised controlled trials (689 patients) and showed that probiotic administration was associated with a lower incidence of VAP when compared with standard care (odds ratio = 0.61; 95% confidence interval = 0.31 to 0.91) [55]. Importantly, both of these were published before the studies by Morrow and colleagues [38], Oudhuis and colleagues [52] and Barraud and colleagues [52].

The trial by Morrow and colleagues is unique in that it included oropharyngeal slurry as one of the routes of administration for the probiotic [38]. The research group randomised 146 ventilated patients who were considered at high risk for VAP to receive probiotic *L. rhamnosus* GG or placebo (inulin) within 24 hours of intubation until extubation, tracheostomy or death. The primary outcome was microbiologically confirmed VAP based on quantitative culture of distal airway samples obtained by bronchoscopy. The incidence of VAP was significantly reduced in the probiotic group (19.1% with probiotic vs. 40.0% with placebo, $P = 0.007$).

Morrow and colleagues also examined the incidence of *Clostridium difficile* and ICU-associated diarrhoea in their patients. The probiotic group had significantly less *C. difficile* cytotoxin-positive diarrhoea compared with the placebo group (5.6% vs. 18.6%, $P = 0.02$), although the duration of diarrhoea was not significantly lower. However, patients treated with probiotic received fewer days of antibiotics for *C. difficile*-associated diarrhoea (0.5 ± 2.3 days vs. 2.1 ± 4.8 days in placebo group, $P = 0.02$). The duration of ICU-associated diarrhoea was also significantly reduced in the probiotic group (4.1 ± 3.7 days vs. 5.9 ± 3.8 days in placebo group, $P = 0.03$).

The rates of oral colonisation with pathogenic species at 72 hours (70% for placebo vs. 38.2% for *Lactobacillus*, $P < 0.001$) correlated with development of VAP (Pearson correlation coefficient = 0.22, $P = 0.009$). Interestingly, the probiotic treatment appeared to preferentially reduce rates of infection caused by Gram-negative pathogens (22.8% for placebo vs. 8.8% for *Lactobacillus*, $P = 0.02$) while having no statistically significant effect on Gram-positive species (12.8% vs. 5.8%, $P = 0.16$).

To date, studies of probiotics in the critically ill have trialled a number of species, *Lactobacillus* featuring frequently. Currently unknown, however, is whether one species is superior in the prevention of infection associated with critical illness. Similarly, the optimal administration route, dosage and duration of treatment are not clear. Further research is undoubtedly warranted, perhaps considering Gram-negative probiotic species.

Administration of probiotics and monitoring of their effects

Probiotics are commercially available in various preparations including yoghurt-based products, capsules, powders and suspensions. The studies in critically ill patients discussed above involve enteral administration of a variety of probiotic strains using different dosing regimes.

In eight of the nine studies involving mechanically ventilated patients (Table 3), probiotic powder or capsule contents were dissolved in water and delivered via a feeding tube into the stomach. Morrow and colleagues used an oropharyngeal slurry of *L. rhamnosus* GG (suspended in a sterile water-based surgical lubricant) in addition to nasogastric administration [38]. After 72 hours, the patients receiving this regime were found to have lower rates of oral (38.2% vs. 70%, $P = 0.001$) and gastric (32.3% vs. 45.7%, $P = 0.03$) colonisation with pathogenic species than those receiving placebo. Klarin and colleagues used topical application of Lp299 to the oral cavity alone and found it to be at least as effective as chlorhexidine 0.1% in reducing oropharyngeal pathogenic load [50].

Testing for colonisation of the gastrointestinal tract with the probiotic species is reported in only a minority of studies. McNaught and colleagues collected gastric aspirates at induction of anaesthesia in elective surgical patients who had received at least 1 week of oral Lp299 [24]. The probiotic species was not isolated in any subject. In the study by Forestier and colleagues, however, gastric aspirates were taken at inclusion, at day 7 and at discharge. *Lactobacillus casei rhamnosus* was detected in 52 out of 102 patients on probiotic treatment after a median of 13 days [49]. In the study by Klarin and colleagues described above, the probiotic species Lp299 was detected in all oropharyngeal cultures and in the tracheal cultures from 56% of patients in the probiotic arm [50]. Knight and colleagues demonstrated detection of probiotic species in stool culture after 3 days treatment with Synbiotic 2000 Forte, indicating its survival from the stomach to the distal gut [56]. However, they did not routinely analyse stool samples in their more recent study [51]. None of the other studies cited in Table 3 reported detection of probiotic species in any microbiological specimens.

Quality and safety

Probiotics are now widely available and are being consumed daily in large quantities. Overall they have an excellent safety record, but there are some concerns that are likely to lead to caution in their widespread use in clinical practice.

The availability of different probiotics varies from country to country and there can be lack of consistency between manufacturers, and even batches, in terms of density of bacteria, adhesion characteristics, stability and viability [57]. Strain-specific adhesion properties and viability have been shown to vary between batches from the same manufacturer, which could lead to conflicting clinical trial results [58].

There have been a number of publications reporting serious infections caused by *Lactobacillus* spp. related to those used as probiotics [59]. The Finnish group of Salminen and colleagues examined 89 cases of *Lactobacillus* bacteraemia. In 11 cases, the strain was identical with the probiotic *L. rhamnosus* GG [60]. However, they could not directly relate these cases to probiotic consumption. Salminen and colleagues also examined trends in *Lactobacillus* bacteraemia in Finland over the period 1990 to 2000. This period coincided with a rapid increase in the consumption of probiotic *L. rhamnosus* GG. The group concluded that increased probiotic use had not led to an increase in *Lactobacillus* bacteraemia [61].

There are case reports in the literature of *Lactobacillus* infection and bacteraemia that appear to be directly related to probiotic consumption [62–65]. All of the patients involved were immunocompromised to some degree and the causative organism was linked to the probiotic by molecular techniques. Infections caused by *Lactobacillus* spp. from probiotics have also been reported in immunosuppressed patients – including those with acquired immunodeficiency syndrome and those following lung and liver transplantation [66–68]. *Lactobacillus* bacteraemia has been associated with structural heart abnormalities, valve prosthesis or prior endocarditis [69]. However, the majority of clinical trials using *Lactobacillus* spp. probiotics report few adverse effects.

The only reported infection associated with probiotic *E. coli* Nissle 1917 is in a premature neonate (gestational age 28 weeks) [70]. The child had an extremely low birth weight of 935 g and developed gastroenteritis due to rotavirus and adenovirus 14 days into the postnatal period. *E. coli* Nissle treatment initially led to improvement but the child developed severe sepsis 10 days later and subsequently *E. coli* Nissle 1917 was isolated in blood cultures. The child was treated with antibiotics and made a full recovery.

A wide range of probiotic species is being investigated for an increasing number of indications. There has been little work carried out on the rationale behind which probiotics are used and in what combination. Timmerman and colleagues attempted to address this issue by examining specific strains in an attempt to produce an effective multispecies mixture [71]. The symbiotic preparation Ecologic 641 was used in the PROPATRIA trial. This group selected six strains of *Lactobacillus* based on survival in a simulated gastrointestinal environment, antimicrobial activity and ability to induce IL-10, highlighting the point that there should be a disease-specific rationale for selection of probiotics.

Conclusions

Concerns are mounting about multidrug-resistant Gram-negative bacteria with the extensive spread of extended-spectrum β-lactamases [72], and in particular the emergence of *Enterobacteriaceae* with resistance to carbapenems conferred by metallo-β-lactamase NDM-1 [73]. New antimicrobial agents with which to tackle resistant bacteria are in limited supply, and a recently announced EU–US taskforce has called for a commitment to the development of 10 new antibacterial agents by 2020. This will require a substantial public financial investment and will need to be sustained long term because continued antibiotic use will maintain the pressure on organisms to evolve new resistant strains. In the absence of universally effective treatments, strategies that could prevent the development of ICU-acquired infection are needed.

The human, animal and *in vitro* studies of probiotics carried out to date exhibit a high level of heterogeneity in the conditions targeted, models used and probiotics tested. These studies are likely to reflect an oversimplistic view of the mechanisms of action of probiotic species. As alluded to above, probiotics are likely to bring about their effects through multiple processes with different strains having very specific effects.

We are still far from understanding fully the probiotic–host interaction but, given the potential benefits that probiotic bacteria have to offer, further study is warranted. Careful consideration should be given to further well-powered studies addressing the questions of which probiotic by what route, in what dose and at what time.

Abbreviations

IL, interleukin; Lp299, *Lactobacillus plantarum* 299; NF, nuclear factor; TNF, tumour necrosis factor; VAP, ventilator-associated pneumonia.

Competing interests

The authors declare that they have no competing interests.

Author details

[1]Academic Department of Anaesthesia, Critical Care and Pain, Heart of England NHS Foundation Trust, Birmingham Heartlands Hospital, Bordesley Green East, Birmingham B9 5SS, UK. [2]ACCS Anaesthetics, Derriford Hospital, Plymouth NHS Trust, Derriford Road, Plymouth, PL6 8DH, UK. [3]Perioperative, Critical Care and Trauma Trials Group, School of Clinical and Experimental Medicine, University of Birmingham, Birmingham B15 2TT, UK. [4]West Midlands Public Health Laboratory, Heart of England NHS Foundation Trust, Bordesley Green East, Birmingham B9 5SS, UK. [5]School of Immunity and Infection, The Medical School, University of Birmingham, Edgbaston B15 2TT, UK.

Published: 5 November 2012

References

1. Alverdy JC, Laughlin RS, Wu L: **Influence of the critically ill state on host–pathogen interactions within the intestine: gut-derived sepsis redefined.** *Crit Care Med* 2003, **31:**598-607.
2. Bengmark S: **Synbiotics to strengthen gut barrier function and reduce morbidity in critically ill patients.** *Clin Nutr* 2004, **23:**441-445.
3. MacFie J, O'Boyle C, Mitchell CJ, Buckley PM, Johnstone D, Sudworth P: **Gut origin of sepsis: a prospective study investigating associations between bacterial translocation, gastric microflora, and septic morbidity.** *Gut* 1999, **45:**223-228.
4. Hassoun HT, Kone BC, Mercer DW, Moody FG, Weisbrodt NW, Moore FA: **Post-injury multiple organ failure: the role of the gut.** *Shock* 2001, **15:**1-10.
5. Sherman PM, Ossa JC, Johnson-Henry K: **Unraveling mechanisms of action of probiotics.** *Nutr Clin Pract* 2009, **24:**10-14.
6. Guarner F, Khan AG, Garisch J, Eliakim R, Gangl A, Thomson A, *et al.*: **World gastroenterology organisation global guidelines: probiotics and prebiotics october 2011.** *J Clin Gastroenterol* 2012, **46:**468–481.
7. Gibson GR, Roberfroid MB: **Dietary modulation of the human colonic microbiota: introducing the concept of prebiotics.** *J Nutr* 1995, **125:**1401-1412.
8. Arumugam M, Raes J, Pelletier E, Le Paslier D, Yamada T, Mende DR, Fernandes GR, Tap J, Bruls T, Batto J-M, Bertalan M, Borruel N, Casellas F, Fernandez L, Gautier L, Hansen T, Hattori M, Hayashi T, Kleerebezem M, Kurokawa K, Leclerc M, Levenez F, Manichanh C, Nielsen HB, Nielsen T, Pons N, Poulain J, Qin J, Sicheritz-Ponten T, Tims S, *et al.*: **Enterotypes of the human gut microbiome.** *Nature* 2011, **473:**174-180.
9. Qin J, Li R, Raes J, Arumugam M, Burgdorf KS, Manichanh C, Nielsen T, Pons N, Levenez F, Yamada T, Mende DR, Li J, Xu J, Li S, Li D, Cao J, Wang B, Liang H, Zheng H, Xie Y, Tap J, Lepage P, Bertalan M, Batto J-M, Hansen T, Le Paslier D, Linneberg A, Nielsen HB, Pelletier E, Renault P, *et al.*: **A human gut microbial gene catalogue established by metagenomic sequencing.** *Nature* 2010, **464:**59-65.
10. Sepp E, Mikelsaar M, Salminen S: **Effect of administration of Lactobacillus casei strain GG on the gastrointestinal microbiota of newborns.** *Microb Ecol Health Dis* 1993, **6:**309-314.
11. Benno Y, He F, Hosoda M, Hashimoto H, Kojima T, Yamazaki K, Iino H, Mykkanen H, Salminen S: **Effect of Lactobacillus GG yoghurt on human intestinal microecology in Japanese subjects.** *Nutr Today* 1996, **31(Suppl 1):**9s-11s.
12. Fayol-Messaoudi D, Berger CN, Coconnier-Polter M-H, Liévin-Le Moal V, Servin AL: **pH-, lactic acid-, and non-lactic acid-dependent activities of probiotic Lactobacilli against Salmonella enterica Serovar Typhimurium.** *Appl Environ Microbiol* 2005, **71:**6008-6013.
13. Venturi A, Gionchetti P, Rizzello F, Johansson R, Zucconi E, Brigidi P, Matteuzzi D, Campieri M: **Impact on the composition of the faecal flora by a new probiotic preparation: preliminary data on maintenance treatment of patients with ulcerative colitis.** *Aliment Pharmacol Ther* 1999, **13:**1103-1108.
14. Corr SC, Li Y, Riedel CU, O'Toole PW, Hill C, Gahan CGM: **Bacteriocin production as a mechanism for the antiinfective activity of Lactobacillus salivarius UCC118.** *Proc Natl Acad Sci U S A* 2007, **104:**7617-7621.
15. Ng SC, Hart AL, Kamm MA, Stagg AJ, Knight SC: **Mechanisms of action of probiotics: recent advances.** *Inflamm Bowel Dis* 2009, **15:**300-310.
16. Flynn S, van Sinderen D, Thornton GM, Holo H, Nes IF, Collins JK: **Characterization of the genetic locus responsible for the production of ABP-118, a novel bacteriocin produced by the probiotic bacterium Lactobacillus salivarius subsp. salivarius UCC118.** *Microbiology* 2002, **148:**973-984.
17. Medellin-Peña MJ, Wang H, Johnson R, Anand S, Griffiths MW: **Probiotics affect virulence-related gene expression in Escherichia coli O157:H7.** *Appl Environ Microbiol* 2007, **73:**4259-4267.
18. Mack DR, Michail S, Wei S, McDougall L, Hollingsworth MA: **Probiotics inhibit enteropathogenic E. coli adherence in vitro by inducing intestinal mucin gene expression.** *Am J Physiol* 1999, **276:**G941-G950.
19. Walker WA: **Mechanisms of action of probiotics.** *Clin Infect Dis* 2008, **46(Suppl 2):**S87-S91; discussion S144-S151.
20. Allen SJ, Okoko B, Martinez E, Gregorio G, Dans LF: **Probiotics for treating infectious diarrhoea.** *Cochrane Database Syst Rev* 2004 **2:**CD003048.
21. Gatt M, Reddy BS, MacFie J: **Review article: bacterial translocation in the critically ill – evidence and methods of prevention.** *Aliment Pharmacol Ther* 2007, **25:**741-757.
22. Shimizu K, Ogura H, Hamasaki T, Goto M, Tasaki O, Asahara T, Nomoto K, Morotomi M, Matsushima A, Kuwagata Y, Sugimoto H: **Altered gut flora are associated with septic complications and death in critically ill patients with systemic inflammatory response syndrome.** *Dig Dis Sci* 2011, **56:**1171-1177.
23. Inglis TJJ, Sherratt MJ, Sproat LJ, Hawkey PM, Gibson JS: **Gastroduodenal dysfunction and bacterial colonisation of the ventilated lung.** *The Lancet* 1993, **341:**911-913.
24. McNaught CE, Woodcock NP, MacFie J, Mitchell CJ: **A prospective randomised study of the probiotic Lactobacillus plantarum 299V on indices of gut barrier function in elective surgical patients.** *Gut* 2002, **51:**827-831.
25. Anderson ADG, McNaught CE, Jain PK, MacFie J: **Randomised clinical trial of synbiotic therapy in elective surgical patients.** *Gut* 2004, **53:**241-245.
26. Reddy BS, Macfie J, Gatt M, Larsen CN, Jensen SS, Leser TD: **Randomized clinical trial of effect of synbiotics, neomycin and mechanical bowel preparation on intestinal barrier function in patients undergoing colectomy.** *Br J Surg* 2007, **94:**546-554.
27. Nomura T, Tsuchiya Y, Nashimoto A, Yabusaki H, Takii Y, Nakagawa S, Sato N, Kanbayashi C, Tanaka O: **Probiotics reduce infectious complications after pancreaticoduodenectomy.** *Hepatogastroenterology* 2007, **54:**661-663.
28. Rayes N, Seehofer D, Theruvath T, Mogl M, Langrehr JM, Nüssler NC, Bengmark S, Neuhaus P: **Effect of enteral nutrition and synbiotics on bacterial infection rates after pylorus-preserving pancreatoduodenectomy: a randomized, double-blind trial.** *Ann Surg* 2007, **246:**36-41.
29. Kanazawa H, Nagino M, Kamiya S, Komatsu S, Mayumi T, Takagi K, Asahara T, Nomoto K, Tanaka R, Nimura Y: **Synbiotics reduce postoperative infectious complications: a randomized controlled trial in biliary cancer patients undergoing hepatectomy.** *Langenbecks Arch Surg* 2005, **390:**104-113.
30. Sugawara G, Nagino M, Nishio H, Ebata T, Takagi K, Asahara T, Nomoto K, Nimura Y: **Perioperative synbiotic treatment to prevent postoperative infectious complications in biliary cancer surgery: a randomized controlled trial.** *Ann Surg* 2006, **244:**706-714.
31. Rayes N, Seehofer D, Hansen S, Boucsein K, Müller AR, Serke S, Bengmark S, Neuhaus P: **Early enteral supply of lactobacillus and fiber versus selective bowel decontamination: a controlled trial in liver transplant recipients.** *Transplantation* 2002, **74:**123-127.
32. Rayes N, Seehofer D, Theruvath T, Schiller RA, Langrehr JM, Jonas S, Bengmark S, Neuhaus P: **Supply of pre- and probiotics reduces bacterial infection rates after liver transplantation – a randomized, double-blind trial.** *Am J Transplant* 2005, **5:**125-130.
33. Oláh A, Belágyi T, Issekutz A, Gamal ME, Bengmark S: **Randomized clinical trial of specific lactobacillus and fibre supplement to early enteral nutrition in patients with acute pancreatitis.** *Br J Surg* 2002, **89:**1103-1107.
34. Oláh A, Belágyi T, Pótó L, Romics L Jr, Bengmark S: **Synbiotic control of inflammation and infection in severe acute pancreatitis: a prospective, randomized, double blind study.** *Hepatogastroenterology* 2007, **54:**590-594.
35. Besselink MGH, van Santvoort HC, Buskens E, Boermeester MA, van Goor H, Timmerman HM, Nieuwenhuijs VB, Bollen TL, van Ramshorst B, Witteman BJM, Rosman C, Ploeg RJ, Brink MA, Schaapherder AFM, Dejong CHC, Wahab PJ, van Laarhoven CJHM, van der Harst E, van Eijck CHJ, Cuesta MA, Akkermans LMA, Gooszen HG: **Probiotic prophylaxis in predicted severe acute pancreatitis: a randomised, double-blind, placebo-controlled trial.** *Lancet* 2008, **371:**651-659.
36. Vincent JL, Bihari DJ, Suter PM, Bruining HA, White J, Nicolas-Chanoin MH, Wolff M, Spencer RC, Hemmer M: **The prevalence of nosocomial infection in intensive care units in Europe. Results of the European Prevalence of Infection in Intensive Care (EPIC) Study. EPIC International Advisory Committee.** *JAMA* 1995, **274:**639-644.
37. Vincent J-L, Rello J, Marshall J, Silva E, Anzueto A, Martin CD, Moreno R, Lipman J, Gomersall C, Sakr Y, Reinhart K: **International study of the prevalence and outcomes of infection in intensive care units.** *JAMA* 2009, **302:**2323-2329.
38. Morrow LE, Kollef MH, Casale TB: **Probiotic prophylaxis of ventilator-associated pneumonia: a blinded, randomized, controlled trial.** *Am J Respir Crit Care Med* 2010, **182:**1058-1064.
39. **Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia.** *Am J Respir Crit Care Med* 2005, **171:**388-416.
40. Vincent J-L, Sakr Y, Sprung CL, Ranieri VM, Reinhart K, Gerlach H, Moreno R, Carlet J, Le Gall J-R, Payen D: **Sepsis in European intensive care units: results**

of the SOAP study. *Crit Care Med* 2006, **34:**344-353.
41. Kollef MH, Shorr A, Tabak YP, Gupta V, Liu LZ, Johannes RS: **Epidemiology and outcomes of health-care-associated pneumonia: results from a large US database of culture-positive pneumonia.** *Chest* 2005, **128:**3854-3862.
42. Liberati A, D'Amico R, Pifferi S, Torri V, Brazzi L, Parmelli E: **Antibiotic prophylaxis to reduce respiratory tract infections and mortality in adults receiving intensive care.** *Cochrane Database Syst Rev* 2009 **4:**CD000022.
43. de Smet AMGA, Kluytmans JAJW, Cooper BS, Mascini EM, Benus RFJ, van der Werf TS, van der Hoeven JG, Pickkers P, Bogaers-Hofman D, van der Meer NJM, Bernards AT, Kuijper EJ, Joore JCA, Leverstein-van Hall MA, Bindels AJGH, Jansz AR, Wesselink RMJ, de Jongh BM, Dennesen PJW, van Asselt GJ, te Velde LF, Frenay IHME, Kaasjager K, Bosch FH, van Iterson M, Thijsen SFT, Kluge GH, Pauw W, de Vries JW, Kaan JA, *et al.*: **Decontamination of the digestive tract and oropharynx in ICU patients.** *N Engl J Med* 2009, **360:**20-31.
44. Oostdijk EAN, de Smet AMGA, Blok HEM, Thieme Groen ES, van Asselt GJ, Benus RFJ, Bernards SAT, Frénay IHME, Jansz AR, de Jongh BM, Kaan JA, Leverstein-van Hall MA, Mascini EM, Pauw W, Sturm PDJ, Thijsen SFT, Kluytmans JAJW, Bonten MJM: **Ecological effects of selective decontamination on resistant gram-negative bacterial colonization.** *Am J Respir Crit Care Med* 2010, **181:**452-457.
45. García-San Vicente B, Canut A, Labora A, Otazua M, Corral E: **[Selective decontamination of the digestive tract: repercussions on microbiology laboratory workload and costs, and antibiotic resistance trends].** *Enferm Infecc Microbiol Clin* 2010, **28:**75-81.
46. Al Naiemi N, Heddema ER, Bart A, de Jonge E, Vandenbroucke-Grauls CM, Savelkoul PHM, Duim B: **Emergence of multidrug-resistant Gram-negative bacteria during selective decontamination of the digestive tract on an intensive care unit.** *J Antimicrob Chemother* 2006, **58:**853-856.
47. Kotzampassi K, Giamarellos-Bourboulis EJ, Voudouris A, Kazamias P, Eleftheriadis E: **Benefits of a synbiotic formula (Synbiotic 2000Forte) in critically Ill trauma patients: early results of a randomized controlled trial.** *World J Surg* 2006, **30:**1848-1855.
48. Spindler-Vesel A, Bengmark S, Vovk I, Cerovic O, Kompan L: **Synbiotics, prebiotics, glutamine, or peptide in early enteral nutrition: a randomized study in trauma patients.** *JPEN J Parenter Enteral Nutr* 2007, **31:**119-126.
49. Forestier C, Guelon D, Cluytens V, Gillart T, Sirot J, De Champs C: **Oral probiotic and prevention of Pseudomonas aeruginosa infections: a randomized, double-blind, placebo-controlled pilot study in intensive care unit patients.** *Crit Care* 2008, **12:**R69.
50. Klarin B, Molin G, Jeppsson B, Larsson A: **Use of the probiotic Lactobacillus plantarum 299 to reduce pathogenic bacteria in the oropharynx of intubated patients: a randomised controlled open pilot study.** *Crit Care* 2008, **12:**R136.
51. Knight DJW, Gardiner D, Banks A, Snape SE, Weston VC, Bengmark S, Girling KJ: **Effect of synbiotic therapy on the incidence of ventilator associated pneumonia in critically ill patients: a randomised, double-blind, placebo-controlled trial.** *Intensive Care Med* 2009, **35:**854-861.
52. Oudhuis GJ, Bergmans DC, Dormans T, Zwaveling J-H, Kessels A, Prins MH, Stobberingh EE, Verbon A: **Probiotics versus antibiotic decontamination of the digestive tract: infection and mortality.** *Intensive Care Med* 2011, **37:**110-117.
53. Barraud D, Blard C, Hein F, Marçon O, Cravoisy A, Nace L, Alla F, Bollaert P-E, Gibot S: **Probiotics in the critically ill patient: a double blind, randomized, placebo-controlled trial.** *Intensive Care Med* 2010, **36:**1540-1547.
54. Watkinson PJ, Barber VS, Dark P, Young JD: **The use of pre- pro- and synbiotics in adult intensive care unit patients: systematic review.** *Clin Nutr* 2007, **26:**182-192.
55. Siempos II, Ntaidou TK, Falagas ME: **Impact of the administration of probiotics on the incidence of ventilator-associated pneumonia: a meta-analysis of randomized controlled trials.** *Crit Care Med* 2010, **38:**954-962.
56. Knight D, Ala'Aldeen D, Bengmark S, Girling K: **The effect of probiotics on gastrointestinal flora in the critically ill.** *Br J Anaesth* 2004, **92:**307-308.
57. Tuomola E, Crittenden R, Playne M, Isolauri E, Salminen S: **Quality assurance criteria for probiotic bacteria.** *Am J Clin Nutr* 2001, **73:**393S-398S.
58. Clements ML, Levine MM, Ristaino PA, Daya VE, Hughes TP: **Exogenous lactobacilli fed to man – their fate and ability to prevent diarrheal disease.** *Prog Food Nutr Sci* 1983, **7:**29-37.
59. Isakow W, Morrow LE, Kollef MH: **Probiotics for preventing and treating nosocomial infections: review of current evidence and recommendations.** *Chest* 2007, **132:**286-294.
60. Salminen MK, Rautelin H, Tynkkynen S, Poussa T, Saxelin M, Valtonen V, *et al.*: **Lactobacillus bacteremia, clinical significance, and patient outcome, with special focus on probiotic L. rhamnosus GG.** *Clin Infect Dis* 2004, 38:62–69.
61. Salminen MK, Tynkkynen S, Rautelin H, Saxelin M, Vaara M, Ruutu P, *et al.*: **Lactobacillus bacteremia during a rapid increase in probiotic use of Lactobacillus rhamnosus GG in Finland.** *Clin Infect Dis* 2002, 35:1155–1160.
62. Rautio M, Jousimies-Somer H, Kauma H, Pietarinen I, Saxelin M, Tynkkynen S, Koskela M: **Liver abscess due to a Lactobacillus rhamnosus strain indistinguishable from L. rhamnosus strain GG.** *Clin Infect Dis* 1999, **28:**1159-1160.
63. Mackay A, Taylor M, Kibbler C, Hamilton-Miller J: **Lactobacillus endocarditis caused by a probiotic organism.** *Clin Microbiol Infect* 1999, **5:**290-292.
64. Kunz A, Noel J, Fairchok M: **Two cases of Lactobacillus bacteremia during probiotic treatment of short gut syndrome.** *J Pediatr Gastroenterol Nutr* 2004, **38:**457-458.
65. Land M, Rouster-Stecens K, Woods C, Cannon M, Cnota J, Shetty A: **Lactobacillus sepsis associated with probiotic therapy.** *Pediatrics* 2005, **115:**178-181.
66. Abgrall S, Joly V, Derkinderen P, Decré D, Carbon C, Yeni P: **Lactobacillus casei infection in an AIDS patient.** *Eur J Clin Microbiol Infect Dis* 1997, **16:**180-182.
67. Jones SD, Fullerton DA, Zamora MR, Badesch DB, Campbell DN, Grover FL: **Transmission of Lactobacillus pneumonia by a transplanted lung.** *Ann Thorac Surg* 1994, **58:**887-889.
68. Patel R, Cockerill FR, Porayko MK, Osmon DR, Ilstrup DM, Keating MR: **Lactobacillemia in liver transplant patients.** *Clin Infect Dis* 1994, **18:**207-212.
69. Saxelin M, Chuang NH, Chassy B, Rautelin H, Mäkelä PH, Salminen S, Gorbach SL: **Lactobacilli and bacteremia in southern Finland, 1989–1992.** *Clin Infect Dis* 1996, **22:**564-566.
70. Guenther K, Straube E, Pfister W, Guenther A, Huebler A: **Severe sepsis after probiotic treatment with Escherichia coli NISSLE 1917.** *Pediatr Infect Dis J* 2010, **29:**188-189.
71. Timmerman HM, Niers LEM, Ridwan BU, Koning CJM, Mulder L, Akkermans LMA, Rombouts FM, Rijkers GT: **Design of a multispecies probiotic mixture to prevent infectious complications in critically ill patients.** *Clin Nutr* 2007, **26:**450-459.
72. Hawkey PM, Jones AM: **The changing epidemiology of resistance.** *J Antimicrob Chemother* 2009, **64(Suppl 1):**i3-i10.
73. Kumarasamy KK, Toleman MA, Walsh TR, Bagaria J, Butt F, Balakrishnan R, Chaudhary U, Doumith M, Giske CG, Irfan S, Krishnan P, Kumar AV, Maharjan S, Mushtaq S, Noorie T, Paterson DL, Pearson A, Perry C, Pike R, Rao B, Ray U, Sarma JB, Sharma M, Sheridan E, Thirunarayan MA, Turton J, Upadhyay S, Warner M, Welfare W, Livermore DM, *et al.*: **Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: a molecular, biological, and epidemiological study.** *Lancet Infect Dis* 2010, **10:**597-602.
74. Adlerberth I, Ahrne S, Johansson ML, Molin G, Hanson LA, Wold AE: **A mannose-specific adherence mechanism in Lactobacillus plantarum conferring binding to the human colonic cell line HT-29.** *Appl Environ Microbiol* 1996, **62:**2244-2251.
75. Forestier C, De Champs C, Vatoux C, Joly B: **Probiotic activities of Lactobacillus casei rhamnosus: in vitro adherence to intestinal cells and antimicrobial properties.** *Res Microbiol* 2001, **152:**167-173.
76. Otte J-M, Podolsky DK: **Functional modulation of enterocytes by Gram-positive and Gram-negative microorganisms.** *Am J Physiol Gastrointest Liver Physiol* 2004, **286:**G613-G626.
77. Wehkamp J, Harder J, Wehkamp K, Wehkamp-von Meissner B, Schlee M, Enders C, Sonnenborn U, Nuding S, Bengmark S, Fellermann K, Schröder JM, Stange EF: **NF-kappaB- and AP-1-mediated induction of human beta defensin-2 in intestinal epithelial cells by Escherichia coli Nissle 1917: a novel effect of a probiotic bacterium.** *Infect Immun* 2004, **72:**5750-5758.
78. Resta-Lenert S, Barrett KE: **Live probiotics protect intestinal epithelial cells from the effects of infection with enteroinvasive Escherichia coli (EIEC).** *Gut* 2003, **52:**988-997.
79. Meddings J: **The significance of the gut barrier in disease.** *Gut* 2008, **57:**438-440.
80. Sherman PM, Johnson-Henry KC, Yeung HP, Ngo PSC, Goulet J, Tompkins TA: **Probiotics reduce enterohemorrhagic Escherichia coli O157:H7- and enteropathogenic E. coli O127:H6-induced changes in polarized T84 epithelial cell monolayers by reducing bacterial adhesion and cytoskeletal rearrangements.** *Infect Immun* 2005, **73:**5183-5188.
81. Yan F, Polk DB: **Probiotic bacterium prevents cytokine-induced apoptosis in intestinal epithelial cells.** *J Biol Chem* 2002, **277:**50959-50965.
82. Ichikawa H, Kuroiwa T, Inagaki A, Shineha R, Nishihira T, Satomi S, Sakata T:

Probiotic bacteria stimulate gut epithelial cell proliferation in rat. *Dig Dis Sci* 1999, **44:**2119-2123.
83. de Champs C, Maroncle N, Balestrino D, Rich C, Forestier C: **Persistence of colonization of intestinal mucosa by a probiotic strain, Lactobacillus casei subsp. rhamnosus Lcr35, after oral consumption.** *J Clin Microbiol* 2003, **41:**1270-1273.
84. Reissbrodt R, Hammes WP, dal Bello F, Prager R, Fruth A, Hantke K, Rakin A, Starcic-Erjavec M, Williams PH: **Inhibition of growth of Shiga toxin-producing Escherichia coli by nonpathogenic Escherichia coli.** *FEMS Microbiol Lett* 2009, **290:**62-69.
85. Shi HN, Walker A: **Bacterial colonization and the development of intestinal defences.** *Can J Gastroenterol* 2004, **18:**493-500.
86. Akira S, Takeda K, Kaisho T: **Toll-like receptors: critical proteins linking innate and acquired immunity.** *Nat Immunol* 2001, **2:**675-680.
87. Ulisse S, Gionchetti P, D'Alò S, Russo FP, Pesce I, Ricci G, Rizzello F, Helwig U, Cifone MG, Campieri M, De Simone C: **Expression of cytokines, inducible nitric oxide synthase, and matrix metalloproteinases in pouchitis: effects of probiotic treatment.** *Am J Gastroenterol* 2001, **96:**2691-2699.
88. Pathmakanthan S, Li CKF, Cowie J, Hawkey CJ: **Lactobacillus plantarum 299: beneficial in vitro immunomodulation in cells extracted from inflamed human colon.** *J Gastroenterol Hepatol* 2004, **19:**166-173.
89. Borruel N, Carol M, Casellas F, Antolín M, de Lara F, Espín E, Naval J, Guarner F, Malagelada JR: **Increased mucosal tumour necrosis factor alpha production in Crohn's disease can be downregulated ex vivo by probiotic bacteria.** *Gut* 2002, **51:**659-664.
90. Arribas B, Rodríguez-Cabezas ME, Camuesco D, Comalada M, Bailón E, Utrilla P, Nieto A, Concha A, Zarzuelo A, Gálvez J: **A probiotic strain of Escherichia coli, Nissle 1917, given orally exerts local and systemic anti-inflammatory effects in lipopolysaccharide-induced sepsis in mice.** *Br J Pharmacol* 2009, **157:**1024-1033.
91. Kaila M, Isolauri E, Soppi E, Virtanen E, Laine S, Arvilommi H: **Enhancement of the circulating antibody secreting cell response in human diarrhea by a human Lactobacillus strain.** *Pediatr Res* 1992, **32:**141-144.
92. Isolauri E, Juntunen M, Rautanen T, Sillanaukee P, Koivula T: **A human Lactobacillus strain (Lactobacillus casei sp strain GG) promotes recovery from acute diarrhea in children.** *Pediatrics* 1991, **88:**90-97.
93. Teitelbaum JE, Walker WA: **Nutritional impact of pre- and probiotics as protective gastrointestinal organisms.** *Annu Rev Nutr* 2002, **22:**107-138.
94. Shida K, Nanno M, Nagata S: **Flexible cytokine production by macrophages and T cells in response to probiotic bacteria: a possible mechanism by which probiotics exert multifunctional immune regulatory activities.** *Gut Microbes* 2011, **2:**109-114.
95. Takeda K, Suzuki T, Shimada S-I, Shida K, Nanno M, Okumura K: **Interleukin-12 is involved in the enhancement of human natural killer cell activity by Lactobacillus casei Shirota.** *Clin Exp Immunol* 2006, **146:**109-115.
96. Hatcher GE, Lambrecht RS: **Augmentation of macrophage phagocytic activity by cell-free extracts of selected lactic acid-producing bacteria.** *J Dairy Sci* 1993, **76:**2485-2492.
97. Kruis W, Fric P, Pokrotnieks J, Lukás M, Fixa B, Kascák M, Kamm MA, Weismueller J, Beglinger C, Stolte M, Wolff C, Schulze J: **Maintaining remission of ulcerative colitis with the probiotic Escherichia coli Nissle 1917 is as effective as with standard mesalazine.** *Gut* 2004, **53:**1617-1623.

doi:10.1186/cc11382
Cite this article as: Crooks NH, *et al*.: Clinical review: Probiotics in critical care. *Critical Care* 2012, **16:**237.